

The University of Chicago

THE SULFONATION OF 5-PHENYL-
5-ETHYLBARBITURIC ACID

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE PHYSICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR OF
PHILOSOPHY

DEPARTMENT OF CHEMISTRY

1933

By
CALVIN STOCKTON YORAN

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The writer wishes to express his sincere appreciation to Professor Julius Stieglitz for the inspiring guidance in the research described in this paper. The writer is also indebted to Drs. E. W. Lowe and R. W. Johnson for their helpful advice and criticism.



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INTRODUCTION

The earliest theory of narcosis was that proposed by Bibra and Harless¹ shortly after the successful use of ether, chloroform and nitrous oxide as anesthetics. They made a series of experiments on frogs and mammals with ether, ethyl acetate and ethyl chloride. They noted that these and other anesthetics were not only good solvents for ordinary fat but also for the fatty substances in the brain. As an explanation of the narcotic action of these compounds they suggested that the anesthetics might dissolve out of the brain cells certain of their fatty constituents and in this way interfere with the normal cell functions. They even tried to show by experiments that the brains of anesthetized animals weighed less than the unanesthetized but these experiments were of no value.

Hermann² also arrived at the conclusion that narcosis was a result of the solvent action of the narcotics upon the fatty substances in the brain cells. Later he would only admit that the fatty substances, for which the narcotics were solvents, were the site of action of the narcotics. This theory of dissolution of fatty constituents of the brain cells has been shown to be incorrect but it is important as a forerunner to the modern lipid theory which is based upon similar solubility relations.

In 1891, Pohl³ published results showing that the red

¹Cited by H. H. Meyer, Arch. exp. Path. Pharmacol., 42, 109 (1899).

²L. Hermann, Arch. Anat. Physiol. Anat. Abt., 27 (1866); "Lehrbuch d. experimentellen Toxicologie," Hirschwald, Berlin (1874), 279.

³J. Pohl, Arch. exp. Path. Pharmacol., 28, 239 (1891).

blood cells took up more chloroform than the plasma and attributed this to their containing the lipoid bodies, lecithin and cholesterol. He also found more in the brain than in any other tissue.

In 1895 experiments were begun in the laboratory of H. H. Meyer on various narcotics that were known at that time and simultaneously investigations on the permeability of living cells for a variety of substances including narcotics were in progress in Overton's biological laboratory. Both investigators by 1899 had formulated a theory of narcosis which a mutual friend found to be identical. Meyer⁴ published a general statement of the theory supported by a paper of his pupil Baum. Overton's⁵ work was not published until two years later. He agreed with the theory as set forth by Meyer and his experiments included many more compounds than Meyer had investigated.

Meyer set down his fundamental propositions as follows:

1. All chemically indifferent bodies which are soluble in fats or fat-like substances (lipoids) must act as narcotics to living protoplasm in so far as they can become distributed within it.

2. Their action must appear first and most markedly in those cells in whose chemical structure these fat-like substances predominate and form peculiarly essential participants in the cell function.

3. The relative degrees of activity of such narcotics must depend upon their mechanical affinity to the fat-like substances on the one hand and to the other constituents of the body, i.e. water, on the other. Consequently upon the partition coefficient which determines their distribution in a mixture of water

⁴H. H. Meyer, op. cit., 42, 109, 119 (1899).

⁵Overton, "Studien über die Narkose," G. Fischer, Jena (1901).

and a fat-like substance.

Meyer and Overton measured the anesthetic potency of the narcotics which they investigated by placing groups of polywogs in dishes containing varying strengths of the narcotic under examination and found the concentration necessary to destroy certain simple reflexes. In the determination of the distribution coefficients, they dissolved a weighed amount of the narcotic in water and shook the resulting solution with an equal volume of pure olive oil. From an analysis of the aqueous phase, it was possible to determine the distribution between the two phases. Overton considered many more compounds than Meyer and in some cases he was unable to obtain the distribution directly and assumed the ratio of the solubilities in the two liquids to represent the true distribution coefficient.

The parallelism between the narcotic concentration and the distribution coefficient is quite evident in Table I which is taken from the paper by Meyer and Baum⁶. The last column has

TABLE I

Substance	Distribution Coefficient C_{oil}/C_{water}	Narcotic Conc. mol/l. for tadpoles	K
Trional	4.4	0.0013	0.0057
Tetronal	4.0	0.0018	0.0072
Butyl chloral	1.6	0.002	0.0032
Sulfonal	1.1	0.006	0.0066
Bromalhydrate	0.7	0.002	0.0014
Benzamide	0.6	0.002	0.0012
Triacetin	0.3	0.01	0.003
Diacetin	0.23	0.015	0.0034
Chloralhydrate	0.22	0.025	0.0055
Ethyl urethane	0.14	0.025	0.0035
Monacetin	0.06	0.05	0.003
Methyl urethane	0.04	0.4	0.016
Alcohol	0.03	0.5	0.015

⁶Meyer and Baum, Arch. exp. Path. Pharmacol., 42, 119 (1899).

been added by the writer and is the product of the narcotic concentration and the distribution coefficient given in the second and third columns.

Winterstein⁷ has criticised Meyer's theory, maintaining that, granting a general parallelism between narcotic concentration and the distribution coefficients, there is not actual proportionality as Meyer has indicated in his postulates. If the distribution coefficient and the narcotic concentration are inversely proportional, then the product of these values should be constant:

$$\text{Distribution Coefficient} = K \frac{1}{\text{Narcotic Concentration}}$$

The variations in K are quite large but Meyer pointed out that there are serious experimental errors in the determination of the narcotic concentration and that the distribution coefficient between olive oil and water is not a true measure of the distribution of a narcotic between brain lipoid and serum but is the most convenient method available for approximating this value.

Kurt H. Meyer⁸ has interpreted this value K as the narcotic concentration in the brain lipoid necessary for narcosis. His work with volatile anesthetics will be discussed later.

After an investigation of some of the discrepancies noted in connection with Baum's work, H. H. Meyer⁹ published a paper on the effect of temperature on both the narcotic efficiency and the distribution coefficients of some six compounds. His conclusions were that, if increasing the temperature lowers the distribution coefficient, there will be a corresponding lowering of the narcotic efficiency; or, if the distribution coefficient is greater at

⁷Winterstein, H., "Die Narkose," J. Springer, Berlin (1926), 307..

⁸Meyer and Gottlieb-Billroth, Z. Physiol. Chem., 112, 55 (1920).

⁹H. H. Meyer, Arch. exp. Path. Pharmacol., 46, 338 (1901).

higher temperatures, then the narcotic will be more effective at higher temperatures. Table II shows the experimental evidence for these conclusions.

TABLE II

Substance	Narcotic Concentration dilution of normal sol.		Partition Coeff. C_{lip}/C_{water}	
	3 C.	30 C.	3 C.	30 C.
Salicyl amide	1:1300	1:600	2.23	1.40
Benzamide	1:500	1:200	0.67	0.43
Monacetin	1:90	1:70	0.093	0.066
Ethyl alcohol	1:3	1:7	0.024	0.046
Chloralhydrate	1:5	1:250	0.053	0.236
Acetone	1:3	1:7	0.140	0.195

An extension of the lipid theory of Meyer and Overton to volatile anesthetics was made by Kurt H. Meyer working with Gottlieb-Billroth¹⁰ and later with H. Hopff¹¹. As mentioned above, they also calculated the concentration in the brain lipid of the narcotics studied by H. H. Meyer and Overton from their results. The narcotic concentrations for mice were determined in terms of the partial pressure of the anesthetic in the inhaled air. Using the solubility of the anesthetic in olive oil as representing the solubility in the brain lipid, they made a calculation of the concentration of the anesthetic in the brain lipid in mols per liter. This value was found to be as nearly constant as could be

¹⁰Meyer and Gottlieb-Billroth, Z. Physiol. Chem., 112, 55 (1920).

¹¹Meyer and Hopff, op. cit., 126, 281 (1923).

expected in view of the experimental errors involved.

In Table III the narcotic concentrations (C) are expressed in volume per cents, so that 370 means 3.7 atmospheres for methane; 80 means an air oxygen mixture containing 80 per cent ethylene. The solubility in olive oil (L) was determined and is given in cubic centimeters of gas per 100 c.c. of fluid. The concentration in the brain lipid ($C_{lip.}$) was calculated from the following equation:

$$C_{lip.} = \frac{C \times L}{24 \times 100}$$

where 24 is the volume of 1 mol of gas at 760 mm. and 20 C.

TABLE III

Substance	L	C	$C_{lip.}$
	Sol. of gas in cc. per 100 cc. olive oil	Conc. of gas in in air- gas mixture	Calc. conc. in brain lipoid
Methane	0.54	370	0.08
Ethylene	1.3	80	0.04
Nitrous oxide	1.4	100	0.06
Acetylene	1.8	65	0.05
Dimethyl ether	11.6	12	0.06
Methyl chloride	14.0	6.5	0.07
Ethylene oxide	31	5.8	0.07
Ethyl chloride	40.5	5.0	0.08
Diethyl ether	50	3.4	0.07
Amylene	65	4.0	0.10
Methylal	75	2.8	0.08
Ethyl bromide	95	1.9	0.07
Dimethyl acetal	100	1.9	0.06
Diethyl formal	120	1.0	0.05
Dichlorethylene	130	0.95	0.05
Carbon disulfide	160	1.1	0.07
Chloroform	265	0.5	0.05

They call attention to their calculated figure for the concentration of chloroform in the brain lipid given as 0.05 (for mice) and compare it with the analysis made on the grey and white matter of dogs anesthetized with chloroform by Frisson and Nicloux¹²

¹²Frisson and Nicloux, Compt. rend. soc. biol., 63, 220 (1907).

which gave the value 0.04.

The experimental results given in the three tables are H. H. Meyer's chief arguments for his theory and the evidence is very good considering the difficulties involved in such work. Many other investigators have attempted to confirm and extend Meyer's work but conflicting results have been obtained. None have made exact repetitions of Meyer's experiments and many have not worked as carefully. A few of the papers will be cited which give evidence bearing upon Meyer's postulates.

Mansfield¹³ showed that chloral and paraldehyde were more effective as narcotics in starved, fat poor animals than in fat ones.

Harass¹⁴ studied a series of amides most of which, however, were not in their pharmacological effects true narcotics, as the narcotic stage was preceded by convulsions in some cases in rabbits. The threshold values were obtained by placing frogs in solutions of varying strength.

TABLE IV

Substance	Distribution Coefficient C_{oil}/C_{water}	Threshold value Conc. mol./l.
Valerdiethyl amide	5.7965	0.00584
Valerdimethyl amide	0.4163	0.0196
Valer amide	0.313	0.111
Valerethylamide	0.2536	0.02
Lactdiethylamide	0.154	0.142
Sodium salicylate	0.018	0.25

Some parallelism between the distribution coefficient and the threshold value is evident here but it is not good.

¹³Mansfield, Arch. intern. de pharmacodynamie, 15, 467 (1905), 17, 343 (1907).

¹⁴Harass, Arch. intern. de pharmacodynamie, 11, 431 (1903).

Frey¹⁵ was able to show some parallelism between narcotic potency and the oil-water distribution coefficient in the injection of hypnotics in rabbits. Again the parallelism is not perfect.

TABLE V

Substance	Distribution Coefficient C_{oil}/C_{water}	Threshold value Conc. mol./l.
Aceton chloroform	14.78	0.000909
Isopral	9.59	0.00140
Butyl chloral	2.25	0.002
Chloran	1.97	0.00125
Dormiol	0.515	0.02307
Chloralhydrate	0.22	0.0333

Von Eeckhout¹⁶ determined the narcotic concentration for polywogs and distribution coefficients for several ureas and amides and these results are given in Table VI.

TABLE VI

Coefficient		Substance	Threshold value per liter
Order	Value		
1	1.90	Methylethylbromacetyl urea	0.00033
2	1.33	α Bromisovalerianyl urea	0.0005
3	1.05	α Iodoisovalerianyl urea	0.00092
5	0.78	α Chloroisovalerianyl urea	0.001
8	0.6454	α Bromvalerianyl urea	0.001
10	0.0487	Valerianyl urea	0.0011
4	0.9263	α Bromisobutyryl urea	0.0025
11	0.3718	α Brombutyryl urea	0.0028
9	0.63	α Bromisovaleramide	0.005
7	0.689	Isovalerianyl urea	0.007
6	0.71	α Bromisobutyramide	0.25
12	0.24	α Brombutyramide	0.03

¹⁵

Frey, op. cit., 13, 445 (1904).

¹⁶

Von Eeckhout, Arch. exp. Path. Pharmacol., 57, 338 (1907).

There is little parallelism between the distribution coefficient and threshold value evident in this table but only two or three of the substances are truly narcotics for mammals and several are quite poisonous.

Fruh¹⁷ also experimented with a long series of narcotics on frogs immersed in their solutions. He did not determine the distribution coefficients himself but took the values from the literature. There is very little parallelism evident in his results.

In none of the above attempts to extend the Meyer-Overton data is there sufficient evidence to either confirm or deny the theory.

Conflicting results have appeared in the literature in the attempts to confirm Meyer's observation on the effect of temperature on narcotic efficiency and distribution coefficients.

Moral¹⁸ in experiments with skeletal nerves found that the effect of alcohol, chloral, monacetin and salicyl amide changed with the temperature as with Meyer's change in partition coefficient.

Unger¹⁹ confirmed Meyer's work for chloral and salicyl amide on polywogs but not on the fish Lenciscus.

Hartman²⁰ working with Cladocera could not confirm Meyer's results.

Bierich²¹ failed to confirm Meyer's results on polywogs with benzamide and salicylamide but the change of temperature was

¹⁷ H. Fruh, op. cit., 95, 129 (1922).

¹⁸ H. Moral, Pflugers Arch. ges. Physiol., 171, 469 (1918).

¹⁹ R. Unger, Biochem. Z., 89, 238 (1918).

²⁰ O. Hartman, Pflugers Arch., 170, 585 (1918).

²¹ R. Bierich, op. cit., 174, 202 (1918).

rapid. He confirmed the change of distribution coefficient with temperature using cod liver oil instead of olive oil.

Höber²² studied the effects of narcotics on the irritability of muscle and the conductivity of nerves at varying temperatures. His results oppose those of Meyer.

Redonnet²³ could not observe a corresponding change with temperature in narcotic potency and partition coefficient of neuronal and adalin.

Denneck²⁴ found both chloral and salicylamide more potent at 30 than at lower temperatures.

Knafl-Lenz²⁵ confirm the parallelism of change of the partition coefficient and the narcotic potency with temperature for salicylamide and benzamide. Chloretone like acetone was found to show the reverse effect.

Von Issekutz²⁶ injected frogs with salicylamide, half the group were cooled in snow, the other half put in a thermostat and the groups were exchanged at the end of an hour. The depth of the narcosis diminished on raising the temperature but with chloral and urethane it remained the same. There was always less salicylamide in the brains of the cooled frogs though they appeared to be more narcotized.

Collet²⁷ working with benzamide, salicylamide and chloral as narcotics on *Loligo* and *Gonionemus* confirmed Meyer's results.

Again with such conflicting results it is impossible to

²² R. Höber, op. cit., 174, 218 (1918).

²³ T. Redonnet, Arch. exp. Path. Pharmacol., 84, 339 (1918).

²⁴ G. Denneck, Biochem. Z., 102, 251 (1920).

²⁵ E. v. Knafl-Lenz, op. cit., 105, 88 (1920).

²⁶ B. v. Issekutz, Pflüger's Arch. ges. Physiol., 202, 371 (1924)

²⁷ M. E. Collet, Proc. Soc. Exp. Biol. Med., 20, 259 (1922).

either prove or disprove the Meyer-Overton theory. Perhaps the most serious criticism of the lipid theory is that it is too simple. The relationship between narcotic efficiency and the distribution coefficient between oil and water as demonstrated by Meyer's work might well account for the transportation of the narcotic to the brain lipid, the "site of action." The action within the brain cells has been explained by Meyer as a loose physical-chemical combination of the narcotic and the lipid which prevents the lipid from carrying out its normal cell function. This is, of course, rather an indefinite and not entirely satisfactory explanation.

The discussion above has been limited to the lipid theory and the other important theories have been neglected. Winterstein²⁸ in his book on narcosis discusses the important theories of narcosis and gives an excellent bibliography. Henderson²⁹ has also written a very complete review of the important theories of narcosis. Henderson finds that none of the existing theories are entirely satisfactory but is of the opinion that the lipid theory has fewest shortcomings and is the best guide we have at present.

The hypnotics of the barbituric acid series had not been discovered at the time of the work of Meyer and Overton but since that time they have become very important in the field of hypnotics. Tabern and Shelberg³⁰ have recently published the results of their study of the physical and chemical properties of some of the important barbitals. They determined the distribution coefficients as well as the relative hypnotic efficiencies and came to the conclusion that there is a definite parallelism such as

²⁸H. Winterstein, "Die Narkose," J. Springer, Berlin (1926), 307.

²⁹Henderson, *Physiol. Rev.*, 10, 171 (1930).

³⁰Tabern and Shelberg, *J. Am. Chem. Soc.*, 55, 329 (1933).

Meyer had pointed out. Their results are contained in Table VII and the relative efficiency is indicated by (+) as the authors considered that this was the fairest in view of the errors involved.

TABLE VII

Barbiturate	Mol. Wt.	Sol.g. per l.	Distr. Coeff. C_{oil}/C_{water}	Nar. Eff.
Dimethyl	156	2.419	0.066	0
Diethyl (Barbital; Veronal)	184	6.00	0.214	+
Ethyl, 1-propyl (Ipral)	198	1.36	0.73	+
1-Propyl, allyl (component of Allonal)	212	4.02	1.12	+++
Diallyl (Dial)	208	1.465	0.85	++
n-Butyl, ethyl (Neonal)	212	1.90	2.58	+++
sec. Butyl, ethyl	212	1.987	1.36	+++
sec. Butyl, allyl	224	2.16	2.48	++++
n-Amyl, ethyl	226	0.554	2.92	+++
1-Amyl, ethyl (Amytal)	226	0.530	2.895	+++
Ethyl, 1-methylbutyl (Nembutal)	226	1.20	4.4	++++
sec. Butyl, β -bromoallyl (Pernocton)	304	0.684	4.3	++++
Phenyl, ethyl (Phenobarbital; Luminal)	234	0.970	1.34	++
Allyl, methylhexylcarbinyl	280	3.06	0.306	0
Ethyl, methylhexylcarbinyl	267	0.414	0.408	0

Several substitution products of 5-phenyl-5-ethylbarbituric acid were prepared by Adams and Bousquet³¹ and it was found that the introduction of amino or nitro groups in the phenyl ring resulted in the loss of hypnotic activity, while the introduction of chlorine or bromine increased the toxicity although the hypnotic action was retained. Leulier and Postie³² have investigated the effect of the substitution of nitro and amino groups in both 5-phenyl-5-ethylbarbituric acid (Luminal) and 5-phenyl-5-methylbarbituric acid (Rutanol) with respect to the distribution coefficients as well as the hypnotic action. They report some hypnotic

³¹Adams and Bousquet, J. Am. Chem. Soc., 52, 225 (1930).

³²Leulier and Postie, Compt. rend., 193, 1476 (1931).

activity in the nitro and amino derivatives but of a much lower order than the original compounds. They show that this behavior is to be expected from the postulates of the Meyer-Overton theory because the distribution coefficients were found to be much smaller than those of the unsubstituted compounds. Their values for the distribution coefficients of Luminal and the nitro and amino derivatives are 1.65, 0.47 and 0.048 respectively.

The work described in the Experimental Part of the present paper constitutes a part of the research undertaken in the George Herbert Jones Laboratory on the mechanism of hypnosis.³³ This research is being carried out under the direction of Professors Julius Stieglitz and Mary M. Rising³⁴ whose work in this field began some years ago. The pharmacological study of the compounds prepared in the present investigation is being carried out under the direction of Dr. A. L. Tatum, Professor of Pharmacology at the University of Wisconsin, to whom the writer wishes to express his sincere appreciation for the splendid cooperation and constructive criticism in the non-chemical part of this research.

Previous workers^{35,36} have shown that it is possible to nitrate 5-phenyl-5-ethyl barbituric acid directly and it appeared that sulfonation might be accomplished as readily. Sulfonation was studied in order to compare the results with the well-known effect of the introduction of a stronger acid and more stable salt forming groups in arsenicals, such as arsphenamine. In the latter case, the salts of the stronger acids, such as sulpharsphenamine, tryparsamide, etc., show greater penetrating power in

³³ J. Shroyer, Doctorate Dissertation, University of Chicago, 1932.

³⁴ Stieglitz and Rising, J. Am. Chem. Soc., 40, 725 (1918).

³⁵ J. Ranwez, Pharm. Belg., 6, 410, 501 (1924).

³⁶ Adams and Bousquet, J. Am. Chem. Soc., 52, 224 (1930).

reaching the brain and overcoming infection in the spinal cord and the brain as in the treatment of paresis.

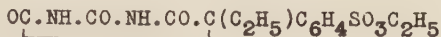
The results of the present study have shown that in the case of phenobarbital as a typical hypnotic, the introduction of a strong acid and stable salt forming group decreases decidedly the hypnotic powers by increasing the water solubility and lowering the solubility in fats. This is in accordance with the Meyer-Overton principle. It indicates clearly that the effect of the arsenicals is apparently chiefly exerted on the protozoa in the aqueous serum of the blood in which they are usually found, whereas hypnosis, in accordance with the current theory require lipid solubility to insure action in the cells.

5-Phenyl-m-sulfonic-acid-5-ethylbarbituric acid $\text{OC.NH.CO.NH.CO.C(C}_2\text{H}_5)_2\text{C}_6\text{H}_5\text{SO}_3\text{H}$ was first prepared and converted into its mono-sodium salt for pharmacological investigations. In doses corresponding to the lethal dose for phenobarbital no narcotic effect was observed. A 1 per cent water solution containing sodium carbonate was given to rabbits intraperitoneally in doses of 223 mg. per kilogram while 150 mg. per kilogram is the lethal dose for phenobarbital. Since the solubility of the sulfonic acid derivative in water is so great and the lipid solubility is very small, it was not possible to determine the distribution coefficient but it must necessarily be extremely small.

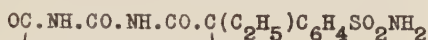
Since the sulfonic acid of phenobarbital was apparently too soluble in water and not soluble enough in lipid, it seemed possible that some of the derivatives of the acid might be found which would have more favorable properties and show hypnotic action. It was found that 5-phenyl-m-sulfonyl-chloride-5-ethylbarbituric acid, $\text{OC.NH.CO.NH.CO.C(C}_2\text{H}_5)_2\text{C}_6\text{H}_5\text{SO}_2\text{Cl}$, could be obtained directly by the action of chlorosulfonic acid on phenobarbital.

From the chloride it was possible to obtain the ethyl ester of the sulfonic acid, the amide and several alkyl substituted amides, as follows:

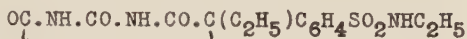
5-Phenyl-m-sulfonic-ethylester-5-ethylbarbituric acid,



5-Phenyl-m-sulfonamide-5-ethylbarbituric acid,



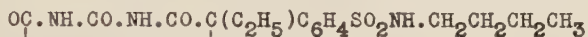
5-Phenyl-m-sulfonethyamide-5-ethylbarbituric acid,



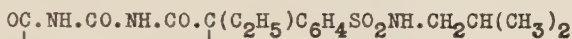
5-Phenyl-m-sulfonallylamide-5-ethylbarbituric acid,



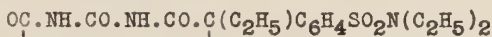
5-Phenyl-m-sulfon-n-butylamide-5-ethylbarbituric acid,



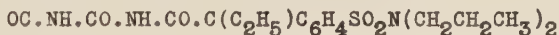
5-Phenyl-m-sulfonisoamylamide-5-ethylbarbituric acid,



5-Phenyl-m-sulfondiethylamide-5-ethylbarbituric acid,



5-Phenyl-m-sulfondi-n-propylamide-5-ethylbarbituric acid,



The sulfonamide derivative of phenobarbital was given to rabbits intraperitoneally in 1 per cent water solutions in doses of 200 mg. per kilogram which again corresponds to the lethal dose for phenobarbital, but no noticeable effect upon the animals was observed. The distribution coefficient of this compound was found to be small and of the order of that found by Leulier and Postie for the amino derivative of phenobarbital, and thus might well account for the absence of any noticeable narcotic effects in doses corresponding to those of the phenobarbital itself.

The alkyl substituted amides, which have not been examined pharmacologically as yet, seem to have more favorable distribution coefficients and it is hoped that hypnotic action will appear in

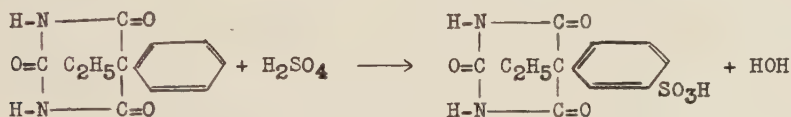
the series as the distribution coefficients become of the order of the other barbitals which have strong hypnotic action. It is expected that the decreased solubility in water and the increased molecular weights as well as the change in chemical constitution will all have some effect upon the hypnotic activity, but it is difficult to predict what the combined effect will be and whether any will show hypnotic action. The solubilities of the important barbitals in water has been given in the table above in connection with the work of Tabern and Shelberg and it will be noted that the solubilities range from 0.5 to 6.0 g. per liter. The solubilities of the compounds under consideration range from about 0.4 for the ethyl ester and the allyl amide, to about 0.02 for the disubstituted amides. The highest molecular weight listed in the same table is that of 5,5-sec. Butyl- β bromoallylbarbituric acid which is 304 and this compound is given as one of the strongest hypnotics in the table. The molecular weights of the compounds prepared range from 339 to 395 which should not have a great deal of an effect in lowering any hypnotic action. The change in chemical constitution would be expected to have the greatest effect upon the hypnotic activity and, since compounds of this type have never been investigated, it is impossible to say what effect this group will have. Amides and substituted amides have been shown to have hypnotic action, but the relative ease of hydrolysis may remove these compounds from Meyer's rather indefinite classification of "indifferent" chemical compounds.

EXPERIMENTAL PART

I. THE SULFONATION OF 5-PHENYL-5-ETHYLBARBITURIC ACID

1. Barium 5-phenyl-m-sulfonate-5-ethylbarbituric acid,

$[OC.NH.CO.NH.CO.C(C_2H_5)C_6H_4SO_3]Ba^{++}$.- Phenobarbital (10 grams) was dissolved in 40 c.c. of concentrated sulfuric acid cooled to 0 C. Fuming sulfuric acid (40 c.c., 30 per cent) was added dropwise to the well cooled and rapidly stirred solution of phenobarbital. Stirring was continued for a few minutes and the solution was tested to show that sulfonation was complete by the addition of a drop of the sulfonation mixture to a few cubic centimeters of cold water in which it dissolved completely if the reaction had gone to completion.



The solution of the sulfonated product in sulfuric acid was poured into 1 liter of ice cold distilled water and treated with an excess of barium carbonate to remove the sulfuric acid leaving the sulfonated product in solution as its dibasic barium salt. The suspension of barium sulfate was filtered and the filtrate concentrated under reduced pressure until crystals of the sulfonate were obtained. The yield was 4.5 g., or 25 per cent of the theoretical yield.

The salt was dissolved in warm water and alcohol was added until a slight cloudiness was observed which was just redissolved with a little more water. White crystals formed very slowly were collected and dried over phosphorus pentoxide in a vacuum desiccator. Analysis of this product by precipitation of barium sulfate

from an aqueous solution gave results over 1 per cent low. This was also checked by a micro method described by Pregl, ignition with sulfuric acid in a platinum boat. These results seemed to indicate that one molecule of water was still retained by the crystals. When the crystals were dried for several hours under a pressure of 2-3 mm. of mercury and at a temperature of 140 C., the last traces of water were driven off.

<u>Anal.</u> Subst., 5.629 mg.	BaSO ₄ , 2.923 mg.
4.568 mg.	2.399 mg.

Calcd. for BaC₁₂H₁₀O₆N₂S : Ba, 30.70%

Found : Ba, 30.56% 30.90%

Oxidation of the compound to the corresponding sulfobenzoic acid to determine the position of the entering group led to the isolation and identification of the meta sulfonic acid of benzoic acid. The yield was very small but low yields appear to be generally met with (see below) in oxidations of this kind. It should be noted, too, that recently M. Rising and Shroyer³⁷ proved that in the nitration of phenobarbital, meta-nitrophenobarbital is the chief and probably the only nitration product.

Preparatory to the oxidation, 10 grams of the sulfonyl chloride derivative (see Part II below), which was obtained more easily, was hydrolyzed with dilute alkali to break up the ureide ring. After the solution in alkali had been heated until ammonia was no longer given off, it was diluted to 600-800 c.c. and small portions of potassium permanganate were added to the solution on a steam bath until a permanent color was obtained. This procedure took several days and when then permanganate color failed to be discharged, the excess was reduced with a little alcohol. The oxides of manganese were removed by filtration and, since it had anticipated that the p-sulfo-benzoic acid would be obtained, conc.

³⁷Rising and Shroyer, Unpublished Work.

hydrochloric acid was added to the filtrate in excess and barium chloride added to precipitate the slightly soluble barium acid salt of p-sulfo-benzoic acid. A heavy precipitate was obtained but this proved to be barium sulfate and corresponded to about 40 per cent of the theoretical yield. In order to isolate any ortho or meta acids, the solution was evaporated almost to dryness with a slight excess of sulfuric acid to free the acids from their salts. The residue was extracted with 95 per cent ethyl alcohol and the alcoholic solution was evaporated to remove any salts still remaining in solution. This residue was again dissolved in alcohol and the excess of sulfuric acid removed by an excess of barium carbonate, leaving the sulfo-acids in solution as their barium salts. The acids were freed by the careful addition of dilute sulfuric acid as long as barium sulfate precipitated. This solution was then evaporated almost to dryness and a small amount (about 1/2 g.) of a crystalline product was obtained. Its melting point was found to be 98 C. After the compound had been dried over phosphorus pentoxide, its melting point was found to be 137-9 C. Tavern³⁸ reports the melting point of meta sulfo-benzoic acid with water of crystallization as 98 C. and for the dry compound, 141 C. with which the melting points of our product agree very well. The oxidation of the sulfonic acid was repeated several times but no better results were obtained. Although permanganate oxidations of meta compounds were not found described in the literature, it might be noted that the yields for a similar oxidation of ortho-toluene sulfonic acid³⁹ was reported to give "extremely low" yields. The exact yields were not reported. The yield of meta nitrobenzoic acid obtained by Rising and Shroyer in

³⁸Tavern, Rec. trav. chim., 25, 53 (1906).

³⁹Brackett and Hayes, Am. Chem. J., 9, 403 (1887).

the oxidation of nitrated phenobarbital was likewise very small. In the absence of any evidence of the formation of the para compound (which would be easily isolated and identified) and clear evidence of the formation of the meta sulfonic acid of benzoic acid, it was concluded that the sulfonic acid group enters in the meta position of the phenobarbital. No evidence of the presence of an ortho derivative was obtained and the physical constants and behavior of all the derivatives of the sulfonic acid prepared precluded the presence of any second acid.

2. 5-Phenyl-m-sulfonic-acid-5-ethylbarbituric acid,
 $\text{OC.NH.CO.NH.CO.C(C}_2\text{H}_5\text{)C}_6\text{H}_4\text{SO}_3\text{H.}$ - The sulfonic acid itself was obtained with great difficulty. An aqueous solution of the dibasic barium salt was treated with dilute sulfuric acid as long as barium sulfate was precipitated and the suspension obtained was filtered. The solution containing the sulfonic acid was evaporated under reduced pressure to dryness. A glassy solid was obtained. This solid residue was dissolved in absolute alcohol without heat and dry ether was added to the solution to precipitate the sulfonic acid. After the solution had stood for several days, crystals appeared which, dried over sulfuric acid in a desiccator, gave a melting point of $130-3^\circ \text{C}$. Analysis for nitrogen by micro-analysis gave consistently low results which checked the value calculated assuming 2 mol H_2O . When the acid was heated at 100° in a vacuum for several hours, it showed a loss of weight of 14.1 per cent (calculated for 2 molecules of water: 10.3 per cent). The melting point of the dehydrated acid was found to be 223°C .

Anal. Subst., 4.234 mg., CO₂, 7.167 mg., H₂O, 1.452 mg.
6.066 mg., CO₂, 10.276 mg., H₂O, 1.891 mg.

3.162 mg., N₂, 0.252 c.c., 23.5°, 747.4mm.
2.248 mg., N₂, 0.178 c.c., 22°, 747.4mm.

Calcd. for C₁₂H₁₂O₆N₂S : C, 46.15%; H, 3.85%; N, 8.98%.

Found: C, 46.17%, 46.20%; H, 3.84%, 3.49%;
N, 9.02%, 9.01%.

3. Mono-sodium-5-phenyl-m-sulfonate-5-ethylbarbituric acid, OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₃Na.- The monobasic sodium salt of the phenobarbital sulfonate was prepared by neutralization of a solution of the acid with sodium hydroxide to the methyl red end point. The solution was concentrated under reduced pressure until crystals of the sodium salt were obtained. The salt was recrystallized from hot water. The yield from 10 g. of phenobarbital was 3 g., or 20 per cent of the theoretical yield. The salt was dried thoroughly at 140° C. in a vacuum. Analyses for carbon, hydrogen, and nitrogen were carried out according to Pregl's micro methods. Analysis for sulfur was made using the standard Parr bomb method. Sodium was determined by a micro method as given by Pregl by igniting the salt with sulfuric acid in a platinum boat and weighing the sodium sulfate.

Anal. Subst., 4.326 mg., CO₂, 6.832 mg., H₂O, 1.377 mg.
5.125 mg., CO₂, 8.094 mg., H₂O, 1.498 mg.

2.998 mg., N₂, 0.222 c.c., 25° C., 736.3mm.
4.548 mg., N₂, 0.333 c.c., 25.5° C., 744.7mm.

0.3435 g., BaSO₄, 0.2374 g.
0.4691 g., BaSO₄, 0.3196 g.

5.442 mg., Na₂SO₄, 1.153 mg.
6.400 mg., Na₂SO₄, 1.340 mg.

Calcd. for C₁₂H₁₁O₆N₂SNa: C, 43.11%; H, 3.29%; N, 8.38%;
S, 9.60%; Na, 6.88%.

Found: C, 43.07%, 43.07%; H, 3.56%, 3.27%; N, 8.22%, 8.21%;
S, 9.49%, 9.36%; Na, 6.78%, 6.86%.

4. Mono-silver-5-phenyl-m-sulfonate-5-ethylbarbituric acid, $\text{OC.NH.CO.NH.CO.C (C}_2\text{H}_5\text{)C}_6\text{H}_4\text{SO}_3\text{Ag}$.- For the preparation of the silver salt of the sulfonic acid, a solution of the acid was divided into two equal parts; and one part was treated with an excess of silver oxide, which yielded the dibasic salt. The two portions were then mixed and the monobasis salt was obtained in crystalline form on evaporation of the mixture under reduced pressure. The salt was recrystallized from hot water.

Anal. Subst., 0.5554 g., AgCl, 0.1827 g.
0.8236 g., AgCl, 0.2714 g.

0.24361g., Loss in drying, 0.00948 g.

Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_6\text{N}_2\text{SAg.H}_2\text{O}$: Ag, 24.63%; H_2O , 4.1%

Found : Ag, 24.77%, 24.80%; H_2O , 3.90%.

II. THE PREPARATION OF 5-PHENYL-m-SULFONYL-CHLORIDE- 5-ETHYLBARBITURIC ACID AND DERIVATIVES

5. 5-Phenyl-m-sulfonyl-chloride-5-ethylbarbituric acid,
 $\text{OC.NH.CO.NH.CO.C (C}_2\text{H}_5\text{)C}_6\text{H}_4\text{SO}_2\text{Cl}$.- Phenobarbital (20 g.) was dissolved in 30 c.c. of chlorosulfonic acid (Eastman's Pract., redistilled). The mixture was heated on a steam bath as long as there was an evolution of hydrochloric acid. The solution was then poured on ice; a white solid separated out. This product was pressed out in a Büchner funnel and dried in a vacuum desiccator over concentrated sulfuric acid. Two recrystallizations from hot glacial acetic acid gave crystals which melted at 226-230° C. The yield was 12 g., or 42 per cent of the theoretical yield. Analyses for carbon, hydrogen and nitrogen were by micro combustion and sulfur and chlorine were determined using Parr bombs.

Anal. Subst., 5.153 mg., CO_2 , 8.195 mg., H_2O , 1.629 mg.
 4.511 mg., CO_2 , 7.224 mg., H_2O , 1.413 mg.

3.871 mg., N_2 , 0.284 c.c., 20° C., 753 mm.
 3.318 mg., N_2 , 0.240 c.c., 19.5°, 751.6 mm.

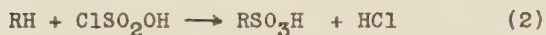
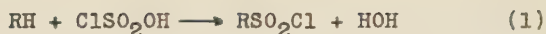
0.2326 g., BaSO_4 , 0.1635 g.
 0.3165 g., BaSO_4 , 0.2278 g.

0.4068 g., AgCl , 0.1790 g.
 0.5017 g., AgCl , 0.2176 g.

Calcd. for $\text{C}_{12}\text{H}_{11}\text{O}_5\text{N}_2\text{SCl}$: C, 43.57%; H, 3.33%; N, 8.47%
 S, 9.70%; Cl, 10.73%.

Found : C, 43.37%, 43.48%; H, 3.53%, 3.50%; N, 8.47%, 8.34%
 S, 9.66%, 9.89%; Cl, 10.88%, 10.73%.

The sulfonation of aromatic compounds with chlorosulfonic acid usually leads to the formation of three compounds: the sulfonyl chloride, the sulfonic acid, and a sulfone, according to the following equations:



Equation (1) represents the reaction desired and this is favored by an excess of the chlorosulfonic acid. In the sulfonation of phenobarbital the sulfone derivative expected from (3) was not isolated and no attempt was made to recover any of the sulfonic acid from (2).

6. 5-Phenyl-m-sulfonic-ethylester-5-ethylbarbituric acid, OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₃C₂H₅.- 5-Phenyl-m-sulfonyl-chloride-5-ethylbarbituric acid (12 g.) was boiled with an excess of absolute ethyl alcohol for several minutes and dissolved completely. The ester was precipitated by the addition of water to the solution until a slight turbidity appeared. The crystals were allowed to form slowly. The product so obtained was recrystallized from alcohol and water in the same manner. The melting point was 176° C. The yield was 5 g., or 40 per cent of the theoretical yield.

The same compound was obtained from the silver salt, described under I, 4, by treatment with ethyl bromide. The mixture was refluxed for an hour and the silver bromide then was separated by filtration. Crystals of the ester were obtained when the excess ethyl bromide evaporated. Their melting point agreed with that of the ester obtained from the sulfonyl chloride and a melting point of a mixture was the same.

Anal., Subst., 6.508 mg., CO₂, 11.795 mg., H₂O, 2.619 mg.
3.010 mg., CO₂, 5.432 mg., H₂O, 1.253 mg.

2.250 mg., N₂, 0.159, 22° C., 751.2 mm.
2.248 mg., N₂, 0.164, 25° C., 743.6 mm.

0.5161 g., BaSO₄, 0.3619 g.,
0.6641 g., BaSO₄, 0.4625 g.

Calcd. for C₁₄H₁₆O₆N₂S : C, 49.41%; H, 4.71%; N, 8.24%;
S, 9.43%.

Found : C, 49.43%, 49.21%; H, 4.50%, 4.66%; N, 8.08%,
8.18%; S, 9.63%, 9.57%.

7. 5-Phenyl-m-sulfonamide-5-ethylbarbituric acid,

OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₂NH₂- 5-Phenyl-m-sulfonyl-chloride-

5-ethylbarbituric acid (12 g.) was treated with 1 to 2 c.c. of concentrated ammonia and the mixture heated on the steam bath for a few minutes. When water was added to the product, the excess of ammonia gave a complete solution of the amide in the form of its ammonium salt. The amide itself was precipitated from its solution by the addition of a slight excess of dilute hydrochloric acid. It was recrystallized from boiling water. Its melting point was 259° C. The yield was 6 g., or 53 per cent of the theoretical yield.

Anal., Subst., 4.538 mg., CO₂, 7.743 mg., H₂O, 1.651 mg.
5.645 mg., CO₂, 9.560 mg., H₂O, 2.031 mg.

3.615 mg., N₂, 0.434 c.c., 27° C., 741.5 mm.
3.652 mg., N₂, 0.430 c.c., 27° C., 743.6 mm.

0.3615 g., BaSO₄, 0.2761 g.
0.6002 g., BaSO₄, 0.4502 g.

Calcd. for C₁₂H₁₃O₅N₃S : C, 46.30%; H, 4.15%; N,
13.19%; S, 10.31%.

Found : C, 46.43%, 46.19%; H, 4.07%, 4.03%; N, 13.28%,
13.06%; S, 10.49%, 10.30%.

III. THE PREPARATION OF SOME ALKYL SUBSTITUTED SULFONAMIDES
OF 5-PHENYL-m-SULFONAMIDE-5-ETHYLBARBITURIC ACID

The method of preparation of the compounds that follow was practically the same and therefore need not be repeated for each compound. 5-Phenyl-m-sulfonyl-chloride-5-ethylbarbituric acid (10 g.) was treated with an aqueous solution of the amine (2/33 mol) corresponding to the amide desired. The products were precipitated from the aqueous solutions of their salts by the addition of dilute hydrochloric acid, and recrystallized from alcohol and water. The yields were about the same as in the case of the amide itself, ranging from 50-60% of the theoretical.

8. 5-Phenyl-m-sulfonethylamide-5-ethylbarbituric acid,
OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₂NHC₂H₅ .- Its melting point is 208° C.
Anal., Subst., 3.901 mg., N₂, 0.430 c.c., 26.5° C., 745.0mm.
1.968 mg., N₂, 0.223 c.c., 30.5° C., 746.1mm.

Calcd. for C₁₄H₁₇O₅N₃S : N, 12.40%.

Found : N, 12.31%, 12.48%.

9. 5-Phenyl-m-sulfonallylamide-5-ethylbarbituric acid,
OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₂NHCH₂CHCH₂.- Its melting point is
184° C.

Anal., Subst., 3.906 mg., N₂, 0.415 c.c., 25.5° C., 738.8 mm.
3.462 mg., N₂, 0.368 c.c., 25° C., 738.8mm.

Calcd. for C₁₅H₁₇O₅N₃S : N, 11.97%

Found : N, 11.81%, 11.84%.

10. 5-Phenyl-m-sulfon-n-butylamide-5-ethylbarbituric acid,
OC.NH.CO.NH.CO.C(C₂H₅)C₆H₄SO₂NHCH₂CH₂CH₂CH₃.- Its melting point
is 190° C.

Anal., Subst., 3.194 mg., N_2 , 0.320 c.c., 27.5° C., 758.3mm.
4.419 mg., N_2 , 0.446 c.c., 27° C., 758.3mm.

Calcd. for $C_{16}H_{21}O_5N_3S$: N, 11.44%.

Found : N, 11.36%, 11.46%.

11. 5-Phenyl-m-sulfonisoamylamide-5-ethylbarbituric acid,

$OC.NH.CO.NH.CO.C(C_2H_5)C_6H_4SO_2NHCH_2CH(CH_3)_2$.- Its melting point is 198° C.

Anal., Subst., 3.248 mg., N_2 , 0.321 c.c., 28° C., 751.8 mm.
4.112 mg., N_2 , 0.408 c.c., 31° C., 751.8 mm.

Calcd. for $C_{17}H_{23}O_5N_3S$: N, 11.03%.

Found : N, 11.09%, 11.02%.

12. 5-Phenyl-m-sulfonydiethylamide-5-ethylbarbituric acid,

$OC.NH.CO.NH.CO.C(C_2H_5)C_6H_4SO_2N(C_2H_5)_2$.- Its melting point is 212 C.

Anal., Subst., 4.113 mg., N_2 , 0.418 c.c., 27° C., 740.5 mm.
2.551 mg., N_2 , 0.263 c.c., 24° C., 740.5 mm.

Calcd. for $C_{16}H_{21}O_5N_3S$: N, 11.44%.

Found : N, 11.27%, 11.54%.

13. 5-Phenyl-m-sulfonydi(n)propylamide-5-ethylbarbituric

acid, $OC.NH.CO.NH.CO.C(C_2H_5)C_6H_4SO_2N(CH_2CH_2CH_3)_2$.- Its melting point is 171 C.

Anal., Subst., 3.603 mg., N_2 , 0.349 c.c., 25.5° C., 739.6mm.
3.624 mg., N_2 , 0.350 c.c., 23° C., 739.6mm.

Calcd. for $C_{18}H_{25}O_5N_3S$: N, 10.64%.

Found : N, 10.78%, 10.84%.

IV. DETERMINATION OF DISTRIBUTION COEFFICIENTS

The distribution coefficients were not determined with any great accuracy for they were used only as a means of comparison within this series of compounds and as a guide in preparing compounds which would be most favorable according to the postulates of the lipoid theory of hypnosis. The solubilities of the compounds used were determined separately in water and olive oil and the ratio of the solubility in olive oil to the solubility in water was assumed to be the distribution coefficient. This is not strictly correct as it applies only to completely immiscible liquids where the solute behaves as a perfect solute and exhibits the same molecular weight in both solvents. The distribution coefficient of phenobarbital was determined in this manner to serve as a check on the method and was estimated to be 1.46. Leulier and Postie⁴⁰ report 1.65 for the distribution coefficient of phenobarbital but do not state how it was determined. Tabern and Shelberg⁴¹ obtained the value 1.34 which they determined by shaking an aqueous solution of the compound with olive oil and then analyzing the aqueous phase for nitrogen by the Kjeldahl method.

The solubility in olive oil (commercial) was determined by suspending a weighed amount of the compound in 100 c.c. of oil warmed slightly. After the suspensions in oil had stood for several days, they were filtered through gooch crucibles with asbestos mats, and washed with low boiling ligoin in which these compounds are very insoluble. The difference in weight gave the solubility.

⁴⁰Leulier and Postie, *Compt. rend.*, 193, 1476 (1931).

⁴¹Tabern and Shelberg, *J. Am. Chem. Soc.*, 55, 329 (1933).

The solubility in water was determined by suspending an excess of the compound in warm water and then allowing the system to reach equilibrium over night. The suspension in water was filtered and titrated with standard barium hydroxide, using phenolphthalien as the indicator. The solubility was calculated from the acidity.

The results obtained are summarized in Table VIII. All compounds given in the table, with the exception of the allyl amide, have been prepared in quantity so that their hypnotic powers may be determined.

TABLE VIII

Derivative of Phenobarbital	Sol. in H ₂ O g./l.	Sol. in Oil g./l.	Distribution Coefficient Sol. in Oil/Sol. in Water
Phenobarbital	1.02	1.50	1.46
Sulfonic ethyl ester	0.384	0.075	0.2
Sulfonamide	0.309	0.02	0.06
Sulfonethylamide	0.275	0.009	0.03
Sulfonallylamide	0.328	0.079	0.24
Sulfon-n-butylamide	0.078	0.058	0.74
Sulfonisoamylamide	0.031	0.118	3.8
Sulfondiethylamide	0.0224	0.034	1.5
Sulfondipropylamide	0.032	0.470	14.6

SUMMARY

1. The lipoid theory of narcosis as developed by Meyer and Overton has been reviewed.

2. Phenobarbital has been sulfonated and its meta sulfonic acid as well as the sodium, barium and silver salts of the acid have been prepared. The sulfonyl chloride derivative of phenobarbital was prepared by sulfonation of the latter with chlorosulfonic acid. The ethyl ester, the amide, and several alkyl substituted amides of the sulfonic acid were prepared from the chloride. The sulfonamides included the ethyl, allyl, n-butyl, iso-amyl, diethyl and dipropyl derivatives.

3. The distribution coefficients in oil and water of the compounds prepared were determined to serve as a guide in the preparation of the most favorable compounds of this series with respect to the postulates of the lipoid theory.

4. The pharmacological of the compounds prepared has not been completed, but preliminary reports show that the sodium salt of the sulfonic acid and the sulfonamide do not appear to be hypnotics of the order of phenobarbital. This is in accord with the predictions of the lipoid theory.

